UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

03/JUN/2008

MEMORANDUM

Subject:	Name of Pesticide Product:	TREE-age
	EPA File Symbol:	100-RGNO
	DP Barcode:	D348524
	Decision No.:	387891
	Action Code:	R310
	PC Code:	128806 (emamectin benzoate)

From: Eugenia McAndrew, Biologist
Technical Review Branch
Registration Division (7505P)

E. McAndrew
Harlow
6-9-08

To: Thomas Harris, RM Team 07
Insecticide -Rodenticide Branch
Registration Division (7505P)

Applicant: Syngenta Crop Protection, Inc.
P. O. Box 18300
Greensboro, NC 27419

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Emamectin benzoate	4.0
Inert Ingredient(s):	96.0
Total:	100.0%

ACTION REQUESTED: The Risk Manager requests review of acute toxicity data for 100-RGNO.

BACKGROUND: Syngenta Crop Protection, Inc. has submitted a six pack of acute toxicity studies to support the proposed product, TREE-age, EPA File Symbol 100-RGNO. The studies were conducted at Eurofins/Product Safety Laboratories, Inc. with assigned MRID numbers 473093-03 to -08. CSFs dated December 13, 2007 for a basic formulation and one alternate formulation are included in the submission. An Agency contractor, Oak Ridge National Laboratory, conducted the primary review of the studies. TRB performed the secondary review and made changes as necessary.

RECOMMENDATIONS: The six studies have been reviewed and are classified as acceptable.

The acute toxicity profile for TREE-age, EPA File Symbol 100-RGNO, is as follows:

Acute oral toxicity	III	Acceptable	MRID 47309303
Acute dermal toxicity	IV	Acceptable	MRID 47309304
Acute inhalation toxicity	IV	Acceptable	MRID 47309305
Primary eye irritation	II	Acceptable	MRID 47309306
Primary skin irritation	IV	Acceptable	MRID 47309307
Dermal sensitization	Negative	Acceptable	MRID 47309308

LABELING: Based on the toxicity profile above, the following are the precautionary and first aid statements for the proposed product as obtained from the Label Review System:

PRODUCT ID #: 000100-01309

PRODUCT NAME: TREE-age

PRECAUTIONARY STATEMENTS

SIGNAL WORD: WARNING

SPANISH SIGNAL WORD: AVISO

Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle.
(If you do not understand the label, find someone to explain it to you in detail.)

Causes substantial but temporary eye injury. Harmful if swallowed. Do not get in eyes or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses). Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before reuse. Wear: Long-sleeved shirt and long pants, socks, shoes, and gloves.

First Aid:

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes.
-Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

If swallowed:
-Call a poison control center or doctor immediately for treatment advice.
-Have person sip a glass of water if able to swallow.
-Do not induce vomiting unless told to by a poison control center or doctor.
-Do not give anything to an unconscious person.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

DATA EVALUATION RECORD

EMMAMECTIN BENZOATE
[EMMAMECTIN BENZOATE ME (042.9) (A16297A)]

STUDY TYPE: ACUTE ORAL TOXICITY - RAT [OPPTS 870.1100; OECD 425]
ACUTE DERMAL TOXICITY - RAT [OPPTS 870.1200; OECD 402]
ACUTE INHALATION TOXICITY - RAT [OPPTS 870.1300; OECD 403]
ACUTE EYE IRRITATION - RABBIT [OPPTS 870.2400; OECD 405]
ACUTE DERMAL IRRITATION - RABBIT [OPPTS 870.2500; OECD 404]
DERMAL SENSITIZATION - GUINEA PIG [OPPTS 870.2600; OECD 406]

MRID 47309303, 47309304, 47309305, 47309306, 47309307, and 47309308

Prepared for
Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202

Prepared by
Toxicology and Hazard Assessment Group
Environmental Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 1-18

Primary Reviewer:
Susan Chang, M.S.

Signature: S. Chang
Date: MAY 08 2008

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: T. Borges
Date: MAY 08 2008

Robert H. Ross, M.S., Group Leader

Signature: R. H. Ross
Date: MAY 08 2008

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: MAY 08 2008

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

Reviewer: ORNL **Date:** April 1, 2008
Risk Manager (EPA): 07

STUDY TYPE: Acute Oral Toxicity – Rat; OPPTS 870.1100; OECD 425

TEST MATERIAL: Emamectin Benzoate ME (042.9) (A16297A) (Emamectin Benzoate, 4.03% w/w; Batch ID 511770; clear blue liquid, specific gravity 1.067 g/mL)

CITATION: Durando, J. (2007) Emamectin Benzoate ME (042.9) (A16297A) – Acute Oral Toxicity Up and Down Procedure in Rats. Study Number 23029. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. December 5, 2007. MRID 47309303.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, Greensboro, NC 27419-8300

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 47309303), nine fasted, young adult female Sprague-Dawley rats (age: 9-11 weeks; body weight: 170-230 g; source: Ace Animals, Inc., Boyertown, PA) were given a single dose of Emamectin Benzoate ME (042.9) (A16297A) (Emamectin Benzoate, 4.03% w/w; Batch ID 511770) as received at doses of 175, 550, 1750, or 5000 mg/kg bw by gavage and observed for 14 days.

All 5000 mg/kg animals died within one day of dosing. All other animals survived the study. One 1750 mg/kg animal had reduced fecal volume on days 2-4 and one 1750 mg/kg animal was hypoactive 5 hours post dosing and had reduced fecal volume on day 1. These animals appeared active and healthy starting on day 2 or 5 until the end of the study. The other surviving animals appeared active and healthy throughout the study. All surviving animals gained weight throughout the study. All decedents were hypoactive and had hunched posture and one decedent had piloerection prior to death. The decedents had red intestines. No gross abnormalities were noted from any surviving animal at necropsy.

Females estimated LD_{50} = 3129 mg/kg bw (Approximate 95% confidence interval is 1750 to 5000 mg/kg bw)

Emamectin Benzoate ME (042.9) (A16297A) is in EPA Toxicity Category III.

This study is classified as acceptable. It does satisfy the guideline requirements for an acute oral study (OPPTS 870.1100; OECD 425) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

AOT425statpgm (Version: 1.0) Test Results and Recommendations
Acute Oral Toxicity (OECD Test Guideline 425) Statistical Program

Date/Time: Monday, March 31, 2008, 2:47:41 PM
Data file name: work.dat
Last modified: 3/31/2008 2:47:39 PM

Test/Substance: Emamectin Benzoate ME (042.9) (A16297A)
Test type: Main Test
Limit dose (mg/kg): 5000
Assumed LD_{50} (mg/kg): Default
Assumed sigma (mg/kg): 0.5

Recommended dose progression: 5000, 1750, 550, 175, 55, 17.5, 5.5, 1.75

DATA:

Test Seq.	Animal ID	Dose (mg/kg)	Short-term Result	Long-term Result
1	3101	175	O	O
2	3102	550	O	O
3	3103	1750	O	O
4	3104	5000	X	X
5	3105	1750	O	O
6	3106	5000	X	X
7	3107	1750	O	O
8	3108	5000	X	X

(X = Died, O = Survived)

Dose Recommendation: The main test is complete.

Stopping criteria met: 5 reversals in 6 tests. LR criterion.

SUMMARY OF LONG-TERM RESULTS:

Dose	O	X	Total
175	1	0	1
550	1	0	1
1750	3	0	3
5000	0	3	3
All Doses	5	3	8

Statistical Estimate based on long term outcomes:

Estimated LD_{50} = 3129 (Based on an assumed sigma of 0.5).
Approximate 95% confidence interval is 1750 to 5000.

Animals were dosed as follows:

Animal Number	Sex	Dose Level (mg/kg)	Long-Term Outcome
3102	F	175	S
3103	F	550	S
3104	F	1750	S
3105	F	5000	D
3106	F	1750	S
3107	F	5000	D
3108	F	1750	S
3109	F	5000	D

S = Survival, D = Death
Animal No. 3101 was dosed at limit dose of 5000 mg/kg. Due to the mortality in this animal, a main test was conducted.

A. **Mortality:** All 5000 mg/kg animals died within one day of dosing. All other animals survived the study.

B. **Clinical observations:** One 1750 mg/kg animal had reduced fecal volume on days 2-4 and one 1750 mg/kg animal was hypoactive 5 hours post dosing and had reduced fecal volume on day 1. These animals appeared active and healthy starting on day 2 or 5 until the end of the study. The other surviving animals appeared active and healthy throughout the study. All surviving animals gained weight throughout the study. All decedents were hypoactive and had hunched posture and one decedent had piloerection prior to death.

C. Gross necropsy: The decedents had red intestines. No gross abnormalities were noted from any surviving animal.

D. Reviewer's conclusions: This reviewer agrees with the study author regarding the acute oral LD_{50}.

Reviewer: ORNL **Date:** April 1, 2008
Risk Manager (EPA): 07

STUDY TYPE: Acute Dermal Toxicity – Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: Emamectin Benzoate ME (042.9) (A16297A) (Emamectin Benzoate, 4.03% w/w; Batch ID 511770; clear blue liquid, specific gravity 1.067 g/mL)

CITATION: Durando, J. (2007) Emamectin Benzoate ME (042.9) (A16297A) – Acute Dermal Toxicity in Rats. Study Number 23030. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. December 5, 2007. MRID 47309304.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, Greensboro, NC 27419-8300

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 47309304), five male and five female young adult Sprague-Dawley rats (age: 9-10 weeks; body weight: males: 275-303 g and females: 189-226 g; source: Ace Animals, Inc., Boyertown, PA) were dermally exposed for 24 hours on an area of approximately 10% of the total body surface area on the clipped dorsal trunk to 5000 mg/kg bw Emamectin Benzoate ME (042.9) (A16297A) (Emamectin Benzoate, 4.03% w/w; Batch ID 511770; pH not reported) as received. The test material was applied evenly over the dose area and covered with a gauze pad. The gauze and the trunk were wrapped with Durapore tape. The animals were observed for 14 days.

All animals survived, and gained weight and appeared active and healthy throughout the study. Erythema and edema were noted on the dose site of two males and two females on day 1. No gross abnormalities were noted at necropsy.

LD_{50} Males > 5000 mg/kg bw
LD_{50} Females > 5000 mg/kg bw
LD_{50} Combined > 5000 mg/kg bw

Emamectin Benzoate ME (042.9) (A16297A) is in EPA Toxicity Category IV.

This study is classified as acceptable. It does satisfy the guideline requirements for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Dose (mg/kg bw)	Mortality/Number Tested		
	Males	Females	Combined
5000	0/5	0/5	0/10

A. Mortality: All animals survived the study.

B. Clinical observations: All animals appeared active and healthy throughout the study. Erythema and edema were noted on the dose site of two males and two females on day 1.

C. Gross necropsy: No gross abnormalities were noted at necropsy.

D. Reviewer's conclusions: This reviewer agrees with the study author regarding the acute dermal LD_{50}.

Reviewer: ORNL **Date:** April 1, 2008
Risk Manager (EPA): 07

STUDY TYPE: Acute Inhalation Toxicity – Rat; OPPTS 870.1300; OECD 403

TEST MATERIAL: Emamectin Benzoate ME (042.9) (A16297A) (Emamectin Benzoate, 4.03% w/w; Batch ID 511770; clear blue liquid)

CITATION: Durando, J. (2007) Emamectin Benzoate ME (042.9) (A16297A) – Acute Inhalation Toxicity in Rats. Study Number 23031. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. December 5, 2007. MRID 47309305.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, Greensboro, NC 27419-8300

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 47309305), five male and five female young adult Sprague-Dawley rats (age: 11-12 weeks; body weight: males: 332-396 g and females: 232-260 g; source: Ace Animals, Inc., Boyertown, PA) were exposed by nose-only inhalation to Emamectin Benzoate ME (042.9) (A16297A) (Emamectin Benzoate, 4.03% w/w; Batch ID 511770) for 4 hours and 1 minute at a concentration of 2.54 mg/L. The animals were then observed for 14 days. The MMADs were 2.5 and 2.6 µm and the GSD 1.83 and 1.85 at 1.5 and 3 hours, respectively.

All animals survived and gained weight during the study. One male had red ocular discharge upon removal from the chamber through day 2. One female was hypoactive and had irregular respiration upon removal from the chamber through day 1. Thereafter, these two animals appeared active and healthy. All other animals were active and healthy throughout the study. No gross abnormalities were noted in any animal at necropsy.

LC_{50} Males > 2.54 mg/L
LC_{50} Females > 2.54 mg/L
LC_{50} Combined > 2.54 mg/L

Emamectin Benzoate ME (042.9) (A16297A) is in EPA Toxicity Category IV.

This study is classified as acceptable. It does satisfy the guideline requirements for an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Nominal Conc. (mg/L)	Gravimetric Conc. (mg/L)	MMAD µm	GSD	Mortality/Number Tested		
				Males	Females	Combined
253.98	2.54	2.5, 2.6	1.83, 1.85	0/5	0/5	0/10

Test Atmosphere / Chamber Description: The exposure atmosphere was generated using a 1/4 inch JCO atomizer (Spraying Systems Co.), FC3 fluid cap (Robert Miller Associates), and 70 SS air cap (Spraying Systems Co.). The test material was metered to the atomization nozzle through Tygon tubing using a pump. Filtered air was supplied by an air compressor connected to the spray atomization nozzle. Additional compressed mixing air from a compressed air tank was introduced into the chamber to help uniformly distribute the test atmosphere. Animals were individually housed in polycarbonate holding rubes which were sealed to the chamber during exposure. The exposure chamber was a Mini Nose-Only Chamber (ADG Developments Ltd.).

Gravimetric Conc. (mg/L):	**2.54**
Chamber Volume (L):	**6.7**
Total Airflow (L/min):	**25.7**
Temperature	**21-23°C**
Relative Humidity	**68-73%**
Time to equilibrium:	**1.2 minutes**

Test atmosphere concentration: During exposure, gravimetric samples were collected six times from the breathing zone of the animals, using glass fiber filters. Filter papers were weighed before and after collection to determine the mass collected. The value was divided by the total volume of air sampled to determine the chamber concentration.

Particle size determination: Particle size for each exposure concentration was determined twice using an eight-stage Andersen cascade impactor. The test material concentration collected at each stage was determined gravimetrically. The mass median aerodynamic diameter and geometric standard deviation were determined graphically using two-cycle logarithmic probit axes.

A. **Mortality:** All animals survived the study.

B. **Clinical observations:** One male had red ocular discharge upon removal from the chamber through day 2. One female was hypoactive and had irregular respiration upon removal from

the chamber through day 1. Thereafter, these two animals appeared active and healthy. All other animals were active and healthy throughout the study. All animals gained weight during the study.

C. Gross necropsy: No gross abnormalities were noted in any animal at necropsy.

D. Reviewer's conclusions: This reviewer agrees with the study author regarding the acute inhalation LC_{50}.

Reviewer: ORNL **Date:** April 1, 2008
Risk Manager (EPA): 07

STUDY TYPE: Primary Eye Irritation – Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: Emamectin Benzoate ME (042.9) (A16297A) (Emamectin Benzoate, 4.03% w/w; Batch ID 511770; clear blue liquid)

CITATION: Durando, J. (2007) Emamectin Benzoate ME (042.9) (A16297A) – Primary Eye Irritation in Rabbits. Study Number 23032. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. December 5, 2007. MRID 47309306.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, Greensboro, NC 27419-8300

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 47309306), 0.1 mL of undiluted Emamectin Benzoate ME (042.9) (A16297A) (Emamectin Benzoate, 4.03% w/w; Batch ID 511770; pH not reported) was instilled into the conjunctival sac of the right eye of three female young adult New Zealand White rabbits (source: Robinson Services, Inc., Clemmons, NC). The untreated eye served as a control. Prior to instillation, 2-3 drops of ocular anesthetic (Tetracaine Hydrochloride Ophthalmic solution) were placed into both the treated and control eye of each animal.The animals were observed for 72 hours and at 4, 7, 10, and 14 days post-instillation.

Corneal opacity was noted on 3/3 rabbits one hour after test material instillation with clearance on one rabbit by 24 hours and on two rabbits by day 14. Iritis was noted on 3/3 rabbits one hour through 24 hours after test material instillation with clearance on one rabbit by 48 hours and on two rabbits by day 14. Positive conjunctival irritation was noted on 3/3 rabbits one hour after test material instillation with clearance on one rabbit by 48 hours, on another rabbit by day 10, and on the third rabbit by day 14. The highest maximum mean total score was 27.7, recorded 24 hours after test material instillation.

In this study, Emamectin Benzoate ME (042.9) (A16297A) was severely irritating. Emamectin Benzoate ME (042.9) (A16297A) is in EPA Toxicity Category II for primary eye irritation.

This study is classified as acceptable. It does satisfy the guideline requirements for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

	Number "positive"/Number treated							
	Hours				days			
Observations	**1**	**24**	**48**	**72**	**4**	**7**	**10**	**14**
Corneal Opacity	3/3	2/3	2/3	2/3	2/3	2/3	2/3	0/3
Iritis	3/3	3/3	2/3	2/3	2/3	2/3	2/3	0/3
Conjunctivae:								
Redness*	3/3	3/3	2/3	2/3	2/3	2/3	1/3	0/3
Chemosis*	3/3	1/3	1/3	1/3	1/3	0/3	0/3	0/3
Discharge**	3/3	3/3	2/3	2/3	0/3	0/3	0/3	0/3

* Score of 2 or more required to be considered "positive"
** Discharge is not a positive effect according to the grading scale

A. **Observations:** Corneal opacity was noted on 3/3 rabbits one hour after test material instillation with clearance on one rabbit by 24 hours and on two rabbits by day 14. Iritis was noted on 3/3 rabbits one hour through 24 hours after test material instillation with clearance on one rabbit by 48 hours and on two rabbits by day 14. Positive conjunctival irritation was noted on 3/3 rabbits one hour after test material instillation with clearance on one rabbit by 48 hours, on another rabbit by day 10, and on the third rabbit by day 14.

B. **Results:** Emamectin Benzoate ME (042.9) (A16297A) was severely irritating. The highest maximum mean total score was 27.7, recorded 24 hours after test material instillation.

C. **Reviewer's conclusions:** This reviewer agrees with the study author that the test material was severely irritating.

Reviewer: ORNL **Date:** April 1, 2008
Risk Manager (EPA): 07

STUDY TYPE: Primary Dermal Irritation – Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: Emamectin Benzoate ME (042.9) (A16297A) (Emamectin Benzoate, 4.03% w/w; Batch ID 511770; clear blue liquid)

CITATION: Durando, J. (2007) Emamectin Benzoate ME (042.9) (A16297A) – Primary Skin Irritation in Rabbits. Study Number 23033. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. December 5, 2007. MRID 47309307.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, Greensboro, NC 27419-8300

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 47309307), three male young adult New Zealand White rabbits (source: Robinson Services, Inc., Clemmons, NC) were dermally exposed to 0.5 mL of undiluted Emamectin Benzoate ME (042.9) (A16297A) (Emamectin Benzoate, 4.03% w/w; Batch ID 511770; pH not reported) for 4 hours on a 6 cm^2 area of the clipped dorsal skin that was covered with a gauze patch. The patch and trunk were wrapped with semi-occlusive Micropore tape. Elizabethan collars were placed on the rabbits. The animals were observed and irritation was scored at 1, 24, 48, and 72 hours after patch removal.

Very slight erythema was noted on 3/3 rabbits 30-60 minutes after patch removal with clearance on one rabbit by 24 hours, on another rabbit by 48 hours, and on the third rabbit by 72 hours.

In this study, the formulation was slightly irritating based on the Primary Irritation Index (PII) of 0.5. Emamectin Benzoate ME (042.9) (A16297A) is in EPA Toxicity Category IV for primary dermal irritation.

This study is classified as acceptable. It does satisfy the guideline requirements for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS and DISCUSSION:

Animal Number	Sex	Hours			
		1	24	48	72
3501	M	1/0[a]	1/0	1/0	0/0
3502	M	1/0	1/0	0/0	0/0
3503	M	1/0	0/0	0/0	0/0
Severity of Irritation – Mean Score		1.0	0.7	0.3	0.0

[a] Erythema/edema

A. Observations: Very slight erythema was noted on 3/3 rabbits 30-60 minutes after patch removal with clearance on one rabbit by 24 hours, on another rabbit by 48 hours, and on the third rabbit by 72 hours.

B. Results: Emamectin Benzoate ME (042.9) (A16297A) was slightly irritating. The Primary Irritation Index (PII) is 0.5.

C. Reviewer's conclusions: This reviewer agrees with the study author that the test material was slightly irritating.

Reviewer: ORNL **Date:** April 1, 2008
Risk Manager (EPA): 07

STUDY TYPE: Dermal Sensitization – guinea pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: Emamectin Benzoate ME (042.9) (A16297A) (Emamectin Benzoate, 4.03% w/w; Batch ID 511770; clear blue liquid)

CITATION: Durando, J. (2007) Emamectin Benzoate ME (042.9) (A16297A) – Dermal Sensitization Study in Guinea pigs (Buehler Method). Study Number 23034. Eurofins/Product Safety Laboratories, 2394 US Highway 130, Dayton, NJ 08810. December 5, 2007. MRID 47309308.

SPONSOR: Syngenta Crop Protection, Inc., 410 Swing Road, Greensboro, NC 27419-8300

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 47309308) with Emamectin Benzoate ME (042.9) (A16297A) (Emamectin Benzoate, 4.03% w/w; Batch ID 511770; pH not reported), 30 female young adult Hartley albino guinea pigs (body weight: 323-380 g; source: Elm Hill Breeding Labs, Chelmsford, MA) were tested using the Buehler Method. The test animals were induced with 0.4 mL of undiluted test material for six hours using occlusive 25 mm Hill Top Chambers that were secured and wrapped with non-allergenic adhesive tape. The procedure was repeated once each week for three consecutive weeks. Twenty-seven days after the first induction, the test animals were challenged with 0.4 mL of undiluted test material under occlusion to naive sites. The naive control animals were treated with 0.4 mL of undiluted test material under occlusion at challenge. Reactions were scored 24 and 48 hours after test material applications.

After three consecutive weekly inductions, no positive dermal reactions were noted from any animal after challenge.

Based on the results of this study, Emamectin Benzoate ME (042.9) (A16297A) was not a dermal sensitizer. The mean challenge scores were 0.00 and 0.03 for naive control and test animals, respectively, at 24 hours and 0.00 for naive control and test animals at 48 hours.

This study is classified as acceptable. It does satisfy the guideline requirements for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the guinea pigs.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

PROCEDURE:

A. **Induction**: The animals were induced and challenged according to the Buehler method. The dorsal and flank areas of 20 test guinea pigs were clipped prior to each treatment. For induction, 0.4 mL of undiluted test material was applied to the animal using an occlusive 25 mm Hill Top Chamber and secured with non-allergenic adhesive tape. The chamber was removed after six hours and excess test material removed. The procedure was repeated once each week for three consecutive weeks. Reactions were scored 24 and 48 hours after the induction applications.

B. **Challenge**: Twenty-seven days after the first induction, the test animals were challenged with 0.4 mL of undiluted test material under occlusion to naive sites for 6 hours. Reactions were scored 24 and 48 hours after challenge application.

C. **Naive control:** The dorsal and flank areas of 10 naive control animals were clipped prior to treatment. At challenge, the naive control group was treated with 0.4 mL of undiluted test material for 6 hours. Reactions were scored 24 and 48 hours following challenge application.

RESULTS and DISCUSSION:

A. **Reactions and durations**: Very faint usually non-confluent erythema was noted on 12/20 test animals over the course of three inductions. Very faint usually non-confluent erythema was noted on 1/20 test animals 24 hours after challenge with clearance by 48 hours. The naive control animals had no irritation after challenge. The test material was not a dermal sensitizer.

B. **Positive control**: The report included the results of a positive control (alpha-hexylcinnamaldehyde) study #21953 conducted within six months of the current study; the results were appropriate.

C. **Reviewer's conclusion**: This reviewer agrees with the study author that the test material was not a dermal sensitizer.

1. **DP BARCODE:** DP348524
2. **PC CODE:** 122806
3. **CURRENT DATE:** April 1, 2008
4. **TEST MATERIAL:** Emamectin Benzoate ME (042.9) (A16297A) (Emamectin Benzoate, 4.03% w/w; Batch ID 511770; clear blue liquid, specific gravity 1.067 g/mL)

Study/Species/Lab Study # / Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Eurofins/Product Safety Laboratories 23029/December 5, 2007	47309303	Females estimated LD_{50} = 3129 mg/kg bw	III	A
Acute dermal toxicity/rat Eurofins/Product Safety Laboratories 23030/December 5, 2007	47309304	LD_{50} Males > 5000 mg/kg bw LD_{50} Females > 5000 mg/kg bw LD_{50} Combined > 5000 mg/kg bw	IV	A
Acute inhalation toxicity/rat Eurofins/Product Safety Laboratories 23031/December 5, 2007	47309305	LC_{50} Males > 2.54 mg/L LC_{50} Females > 2.54 mg/L LC_{50} Combined > 2.54 mg/L	IV	A
Primary eye irritation/rabbit Eurofins/Product Safety Laboratories 23032/December 5, 2007	47309306	Severely irritating	II	A
Primary dermal irritation/rabbit Eurofins/Product Safety Laboratories 23033/December 5, 2007	47309307	Slightly irritating	IV	A
Dermal sensitization/Guinea pig Eurofins/Product Safety Laboratories 23034/December 5, 2007	47309308	Not sensitizing	-	A

Core Grade Key: A = Acceptable, S = Supplementary, U = Unacceptable, W = Waived